CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
SODIUM BROMIDE

Chemical Code # 001103, Tolerance # 50322
SB 950 # 856
Original date: October 31, 2001

I. DATA GAP STATUS

Chronic toxicity, rat:	Data gap, no study submitted.
Subchronic toxicity, rat:	Data gap, inadequate study.
Chronic toxicity, dog:	Data gap, no study submitted
Oncogenicity, rat:	Data gap, no study submitted
Oncogenicity, mouse:	Data gap, no study submitted
Reproduction, rat	Data gap, inadequate study, possible adverse effect indicated
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	Data gap, no study submitted.
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	Data gap, inadequate study, no adverse effect indicated[a]
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.
[a] Study upgradeable
** indicates an acceptable study.
Bold face indicates a possible adverse effect.

File Name: T011031.
Prepared by J. Kishiyama and J. Gee, October 31, 2001

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

"Reregistration Eligibility Decision (RED): Inorganic Halides." (US EPA, September 1993) The conclusion was that exposure to sodium bromide poses negligible risk. The only toxicity studies required were acutes for the formulated products. Since there were, in 1993, no food uses, no tolerances were established. The Agency had genotoxicity studies on file. Based on the use of sodium bromide as a sedative, the human health effects were considered well known. The risk of occupational exposure was considered minimal and risks to humans negligible. (Gee, 10/29/01).

50322 039 143936 Shade, W. D. "Human health risk assessment of sodium bromide (NaBr) for use in cooling water systems, pulp and paper mills and wastewater treatment applications." (Toxicology Department, Rohm and Haas, 12/1/95) The document reviews the exposure potential of workers. On page 8, the chemistry of NaBr products was reviewed. The active biocide is hypobromous acid, released in water in the presence of hypochlorous acid from sodium hypochlorite or chlorine gas. The animal toxicology was reviewed as follows: NaBr is non-irritating and non-sensitizing to skin and slightly irritating to eyes. In the rat developmental study, it was teratogenic at 1000 mg/kg in the presence of maternal toxicity (see record 143932). Bromide salts have been used in sedatives and as anticonvulsants in drugs at doses of 1 gram/day or greater (page 10). In 1988, the Joint Meeting on Pesticide Residues (JMPR) established an ADI of 1 mg/kg/day, based on human oral studies. Using this value, a Time-Weighted Average for inhalation was calculated as 7 mg/m^3. Sodium bromide is not volatile but exposure to dust or aerosol particles is possible. Dermal absorption was described as low, based on polarity. In addition, workers are to be protected by clothing, etc. The highest recommended concentration of sodium bromide for cooling water systems and pulp and paper mills was stated as 3.2 ppm. Even at 5 ppm (5 mg NaBr/liter), daily intake, assuming 2 liters/70 kg body weight, would be 0.14 mg/kg/day, below the ADI. No worksheet. (Gee, 10/22/01)

COMBINED, RAT

No study submitted.

CHRONIC TOXICITY, RAT

No study submitted.

SUBCHRONIC, RAT

50322 - 037 142027 Van Logten, M. J. *et al.* "Semichronic toxicity studies of sodium bromide in rats on a normal diet and a low chloride diet." (National Institute of Public Health, Bilthoven, The Netherlands, publ. in: *Med. Fac. Landbouww. Rijksuniv. Gent.* 41/2: 1499 - 1507 (1976)) Wistar-

SPF rats, 10/sex/group, were fed synthetic diets with 8 g chloride/kg food (normal) or 1 g chloride/kg food (low chloride). Rats on the normal chloride diet received sodium bromide in the diet at 0, 75, 300, 1200, 4800 or 19200 ppm. In the low chloride diet, sodium bromide was 0, 8, 31, 125, 500 or 2000 ppm, both fed for 90 days. Animals at the high doses on both diets showed depressed grooming and motor incoordination of the hind legs. Three/sex died at 2000 ppm, low chloride. Growth at 12 weeks was lower at the high doses of sodium bromide, especially with the low chloride diet. Bromide concentration in plasma reached a plateau after 3 weeks and 8 weeks on the normal and low chloride diets, respectively. Neutrophil granulocytes were increased at the high doses. Bromide levels in brain and kidneys were directly proportional to the diets with a dose $1/10^{th}$ in low chloride diet being comparable to the normal diet. Relative weights for thyroid and adrenals increased at 19200 ppm, both sexes. A summary table of histopathological findings indicated that the thyroid, adrenals, ovaries, and testes were target organs (see also record no. 142030 in 037). In the low chloride group at 2000 ppm, effects were seen in the brain (hyperemia), heart (degeneration of the myocard), others, suggesting that bromide was much more toxic on low chloride diets in rats. Supplemental data. No worksheet. (Gee, 10/22/01)

037 142030 Van Logten, M. J., M. Wolthuis, A. G. Rauws, R. Kroes, E. M. Den Tonkelaar, H. Berkvens and G. J. van Esch. "Semichronic Toxicity of Sodium Bromide in Rats." (National Institute of Public Health, Netherlands, publ. in: *Toxicology* 2: 257 - 267 (1974)) Sodium bromide, 99.5% purity, was admixed with the feed at concentrations of 0, 75, 300, 1200, 4800 and 19200 ppm and fed for 90 days to 10 Wistar-SPF rats/sex/group. High dose (19200 ppm) rats had lower body weight gain, depressed grooming and hind leg incoordination, which remained throughout the study. Relative thyroid weights were increased (1200 ppm and above in females and in high dose males); adrenal weight was increased in high dose males and prostate weight was decreased in the two highest dose groups. The percentage of neutrophils increased in the high dose groups. Histopathological findings indicated possible disruptions of the endocrine system. Bromide levels increased in the plasma, kidney and brain in proportion to the sodium bromide content of the diet. NOEL = 300 ppm (thyroid weight in females) UNACCEPTABLE with numerous deficiencies. (Kishiyama and Gee, 10/26/01).

037 142036 Same study as 037 142027.

CHRONIC TOXICITY, DOG

No study submitted.

ONCOGENICITY, RAT

No study submitted.

ONCOGENICITY, MOUSE

No study submitted.

REPRODUCTION, RAT

037 142029 Van Leeuwen, F. X. R., E. M. Den Tonkelaar and M. J. Van Logten. "Toxicity of Sodium Bromide in Rats: Effects on the Endocrine System and Reproduction." (National Institute of Public Health, publ. in *Fed. Chem. Toxic.* 21(4): 383-389 (1983)) Sodium bromide was fed in the diet at concentrations of 0, 75, 300, 1200, 4800 and 19200 mg/kg of diet to 3 successive generations with 2 litters per generation, except there were three litters in the first generation. The fetuses were used to investigate transplacental transport of bromide. The number of animals/dose/group apparently varied with most groups having 10/sex. At 1200 mg/kg diet and lower concentrations, no consistent treatment-related effects on breeding and offspring were noted. Data from both litters were combined in the report. Dose groups at 4800 mg and 19200 mg/kg diet were eliminated after the first breeding, due to the adverse effects on fertility. At 4800 mg/kg, viability was greater in the second litter. All young alive on day 5 in the first litter died before day 21. To examine whether infertility was due to males or females, animals in the 19200 mg/kg group were mated with untreated animals. Only 20% of treated females mated with untreated males became pregnant and no treated males sired a litter. The conclusion was that both sexes were affected. [In a 90-day study, pathological lesions were seen in both testes and ovaries.] Reversibility was studied by feeding parental animals from the 19200 mg/kg group NaBr for 7 months followed by control diet for 3 months. After mating, the fertility index was 62%, viability index, 61%, and lactation index, 90%. The results indicated that the effect on reproduction was reversible. The authors state that there was no evidence of anomalies. The bromide levels in the kidneys of the fetuses were similar to the maternal levels and increased with increasing concentration in the diets, demonstrating fetal exposure. In a special study, serum levels of thyroxine were determined after 6 and 12 weeks of dosing in F0 parents. There was a significant dose-related decrease in T_4 at 6 weeks with similar results at 12 weeks, indicating an inhibitory effect of bromide on thyroid hormone synthesis with a feed-back for increased TSH by the pituitary and stimulation of the thyroid gland. Uptake of iodine-131 by the thyroid was greater at 500 mg KBr/kg diet than at 2000 mg/kg, measured at 6, 24 and 48 hours, probably reflecting competition of bromide with iodide. Based on the above and a 90-day study, the authors determined the NOEL to be 300 mg/kg diet or 12 mg/kg body weight. Using a safety factor of 100, the ADI would be 0.12 mg/kg body weight or 6 - 7 mg/day for a 60 kg person. POSSIBLE ADVERSE EFFECT (reduced fertility and viability at high doses, depression of thyroxine) . Supplemental information. (Kishiyama and Gee, 10/26/01).

037 142037 Mangurten, H. H. and C. I. Kaye "Neonatal bromism secondary to maternal exposure in a photographic laboratory." (Lutheran General Hospital, publ. in *J. Pediatrics* 100 (4): 596 - 598 (1982)) A case report is described in which an infant had a cyanotic episode on day 4. A number of parameters were normal but urine bromide was 33 mg/dl on day 11 with the reference range being less than 0.25 mg/dl. By day 18, bromide was 15 mg/dl and the hypotonia was improving. At 91/2 months, she had residual mild hypotonia of the neck but speech and social development appeared normal. The mother's occupation involved mixing or using photographic chemicals on a daily basis. Supplemental information. No worksheet. (Gee, 10/29/01)

TERATOLOGY, RAT

** 50322 - 038 143932 Myer, D. P. " Sodium Bromide: Developmental Toxicity (Embryofoetal Toxicity and Teratogenic Potential) Study in Rats (Gavage Administration)". (Huntingdon Research Centre Limited, HRC Project Identity DSB 90/950921, November 20, 1995.) Sodium bromide,

technical grade, 99.84%, was administered by gavage at doses of 0, 100, 300, or 1000 mg/kg/day to 25 mated female rats (Crl: CD® BR VAF/Plus)/group from Day 6 to 15 *post coitum*. High-dose dams became uncoordinated and unkempt in appearance with the effects seen at a higher incidence post-dose. Body weight change was reduced for the high-dose and mid-dose groups (late in gestation only). Maternal NOEL = 100 mg/kg/day (clinical signs, body weight gain). High-dose litters (and fetuses) had increased incidences of visceral (uro-genital system) and skeletal (ribs) malformations and anomalies of the thoracic and cranial area. Mid-dose fetuses had ossification effects related to sternebrae and cranial anomalies. Developmental NOEL = 100 mg/kg/day. The fetal effects were seen in the presence of significant maternal toxicity at 1000 mg/kg/day. ACCEPTABLE. (Kishiyama and Gee, 10/22/01).

037 142028 Harned, B. K. *et al.* "The effect of the administration of sodium bromide to pregnant rats on the learning ability of the offspring. II. Maze-test." (Women's Medical College of Pennsylvania and Temple University, publ. article, site not given, pages 215 - 226, 1944) Wistar-derived female albino rats were given sodium bromide by oral gavage at doses of 0, 40, 80 or 120 mg/kg, days 3 to 20 of gestation. Pups were born approximately two days after the last dose. Pups were untreated with bromide except through the milk. Most were weaned at 20 days of age. From days 20 through 34, pups received 0.2% sodium chloride in drinking water and 0.5%, days 35 through 41. From day 57 - 60, rats were prepared for learning a maze and were given two trials per day, days 61 - 85. Food was the incentive for running the maze. Bromide was quantitated in representative newborns 4 hours after birth and in blood at day 62. The content in newborn was related to the dose given to the dams. Mortality was related to bromide dose, being 2.3% (1/43) in concurrent control, 22.0% (37/168) in laboratory control, 27.0% (17/63) at 40 mg/kg, 41.9% (65/155) at 80 mg/kg, and 58.0% (69/119) at 120 mg/kg, for still births and deaths before day 20 of lactation. At day 62, the bromide content of the pups from exposed mothers was comparable and less than controls, possibly reflecting sodium chloride intake. Test results in the maze, therefore, were not due to bromide content at the time of testing. Growth patterns of all groups were approximately the same. For maze learning, two measurements were compared, errors and time to the goal box of food. Pups from the 120 mg/kg dams had significantly more errors and slower times. At 80 mg/kg, errors may have been greater but times were comparable. However, as a function of days of testing over the 25 days, the 120 mg/kg pups reached the same level of performance by the end of the period. The conclusion of the authors was that the rate of learning was affected by exposure of the dams to bromide rather than the final performance. Supplementary data. No worksheet. (Gee, 10/23/01).

TERATOLOGY, RABBIT

No study submitted.

GENE MUTATION

** 50322 - 026 116069 Jones, E. and L. A. Wilson. "Ames Metabolic Activation Test to Assess the Potential Mutagenic Effect of Sodium Bromide". (Huntingdon Research Centre Limited, Report No. DSB 4/88137, May 20, 1988) Sodium Bromide, purity 98%, was tested at concentrations of 0 (water), 50, 150, 500, 1500 or 5000 µg/plate with and without metabolic activation (S9 Mix) for mutagenic potential using *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100. There were triplicate plates per concentration and two trials. Positive controls were functional.

There was no evidence of mutagenic potential in the study as conducted. ACCEPTABLE. (Kishiyama and Gee, 10/18/01).

CHROMOSOME EFFECTS

50322 - 026 116070 Brooker, P. C., L. C. Akhurst, V. M. Gray and C. Cavaliere. "Sodium Bromide Technical Grade: Metaphase Chromosome Analysis of human Lymphocytes Cultured *In Vitro*. " (Huntingdon Research Centre Limited, Report No. DSB 5/88447, June 7, 1988.) Sodium Bromide Technical, 99.23%, at concentrations of 0, 500.2, 2501, and 5002 µg/ml, was assayed for its ability to induce chromosomal aberrations in human lymphocytes cultured *in vitro*. The high concentration was the maximum achievable based on the solubility of sodium bromide. The lymphocytes were separated from whole blood by gradient centrifugation. The source(s) of the lymphocytes was not given. The cells were stimulated with phytohemagglutinin for 48 hours before treatment in the presence and absence of rat liver metabolic activation. Treatment was for 2 hours with S9 followed by an additional 20 hours of incubation plus two hours with colchicine for a total of 24 hours. Without S9, exposure was for 24 hours. There were two cultures per concentration with 100 cells scored per culture for aberrations, excluding gaps. Sodium bromide treatment did not induce chromosomal aberrations in human lymphocyte cells under test conditions. Positive controls were functional. UNACCEPTABLE but upgradeable (source(s) of the lymphocytes). (Kishiyama and Gee, 10/19/01).

DNA DAMAGE

** 50322 - 026 116071 Henderson, L. M. and R. J. Proudlock. “Assessment of Unscheduled DNA Repair Synthesis in Mammalian Cells after Exposure to Sodium Bromide (Technical Grade)” (Huntingdon Research Centre Limited, Report No. DSB 6/88454, June 8, 1988.) Sodium Bromide technical grade, 99.23%, was evaluated at 12 concentrations ranging from 12.5 to 25600 µg/ml, with and without rat liver activation, for its ability to induce DNA repair in cultured HeLa S3 epithelioid cells. There were duplicate cultures per concentration with two trials. One hundred cells were scored for each culture. At the highest concentration, there was severe inhibition of S-phase replication and grain counts were not scored. The osmolality at the highest concentration was twice the control and may have been a factor. Net nuclear counts were calculated using a single cytoplasmic value. Sodium bromide treatment did not induce a reproducible increase in net grain counts/100 nuclei. ACCEPTABLE. (Kishiyama and Gee, 10/19/01).

MISCELLANEOUS STUDIES

50322 - 037 142026 Sangster, B. *et al.*, " The influence of sodium bromide in man: A study in human volunteers with special emphasis on the endocrine and the central nervous system." (National Institute of Public Health, Bilthoven, and Netherlands Institute for Preventive Health Care-TNO, The Netherlands, published in: *Fd. Chem. Toxic*. 21(4): 409 - 419 (1983)) Groups of male and female volunteers were given sodium bromide in capsules at doses of 0, 4 or 9 mg Br^-/kg/day for 12 weeks (males) or 3

menstrual cycles (females) with 7/sex/group. Measurements included serum and urine bromide, hormone levels for T_4, T_3, free thyroxine, cortisol, progesterone, testosterone, prolactin, LH, FSH, and TSH at termination compared with predosing levels. Central nervous system effects were evaluated using EEG and visual evoked response. Although there were some changes, all values were stated as within normal limits. T_4 and T_3 levels were statistically significantly increased in high dose females. NOEL not determined but 4 mg Br^-/kg/day was suggested from the limited data. Supplemental study. [The study has been considered to demonstrate a NOAEL of 9 mg/kg - see record no. 143936 in 039, page 11] (Gee, 10/22/01).

OTHER

037 142031 Loeber, J. G., M. A. M. Franken and F. X. R. van Leeuwen "Effect of sodium bromide on endocrine parameters in the rat as studied by immunocytochemistry and radioimmunoassay." (National Institute of Public Health, The Netherlands, publ. in *Food Chem. Toxic.* 21 (4): 391 - 404 (1983)) Male Wistar rats (Riv:TOX[M]) weighing 60 to 100 grams were fed diets containing sodium bromide (99.5%) at 0, 20, 75, 300, 1200 or 19,200 mg/kg of diet, 10/group. After 4 or 12 weeks, rats were sacrificed. An additional high dose and control group of 5 were injected with thyrotropin-releasing hormone (TRH) and the serum used for hormone assays. The thyroid, pituitary and testes were weighed and preserved. Immunocytochemistry was used to locate thyroid-stimulating hormone, growth hormone and adrenocorticotropic hormone (ACTH). Radioimmunoassay was used to determine serum levels of these as well as T_4 and testosterone. Body weight was lower at 19200 mg/kg diet after both 4 and 12 weeks. Thyroid weight was increased relative to control at the high dose and at 1200 mg/kg at 4 weeks but not after 12 weeks. Histopathological examination showed activation of the thyroid and decreased spermatogenesis. Thyroxine was decreased and TSH increased at 19200 mg/kg diet. ACTH in the pituitary also increased, insulin increased in serum and corticosterone decreased at the high dose. FSH increased and testosterone decreased. Therefore, at high doses, sodium bromide affects the thyroid, adrenals and testes. The NOEL = 300 mg/kg diet. Supplementary information. No worksheet. (Gee, 10/29/01)

037 142033 Hansen, K. and H. Hubner "Effects of bromide on behavior of mice." (Max von Pettenkofer-Institut des Bundesgesundheitsamtes, Germany, publ. in *Food Chem. Toxic.* 21 (4): 405 - 408 (1983)) Male NMRI mice were fed diets containing sodium bromide (99.5%) at 0, 400, 1200, 3600 or 10,800 ppm on days 43 to 78 of the 128 day total. Motility of mice during the night was measured daily using infra-red light barriers. Evasion time and running behavior on a treadmill were recorded. The motility pattern at 10800 ppm did not follow the control. Motility over the dosing period increased at 3600 and 10800 ppm with a decrease after return to the control diet but with some residual affects at 10800ppm. Evasion time was decreased at all doses and most obvious at the high dose. Treadmill behavior was altered only at the high dose. Body weight at 10800 ppm was lower from the start of dosing until termination of the study. The effect level was between 400 and 1200 ppm sodium bromide in the diet. Supplemental information. No worksheet. (Gee, 10/29/01)

037 142034 Knight, H. D. and M. Reina-Guerra "Intoxication of cattle with sodium bromide-contaminated feed." (University of California, Davis, publ. in *Am. J. Vet. Res.* 38 (3): 407 - 409 (1977)) Holstein-Friesian steer calves and 1 heifer were fed diets containing 170, 511, 1062, 2633 or 4650 ppm bromide from sodium bromide (99.7%) for 49 days followed by 42 days on control diets.

Serum bromide concentration was determined before the start and weekly during the study. Liver, muscle and kidney bromide content were determined from one calf fed the high concentration and the lowest concentration at the end of dosing. One calf at the highest dose was sacrificed after 91 days total. Two additional calves were fed baled oat hay with an average of 7232 ppm bromide ion for 21 days. By day 12 at 4650 ppm, calves had incoordinated movement and gait and had difficulty getting up after falling. At 2633 ppm, calves were incoordinated by day 22. Serum bromide reached a plateau within 21 days of initiation of dosing except at the highest dose. Bromide decreased after ceasing exposure. Serum levels were related to the dose. At the time of appearance of clinical signs, the serum bromide was over 31.25 mEq/L. The calves on contaminated hay also developed clinical signs with serum levels of 34.38 and 40.38 mEq/L. Supplemental information. No worksheet. (Gee, 10/29/01).

037 142035 Vaiseman, N., G. Koren and P. Pencharz "Pharmacokinetics of oral and intravenous bromide in normal volunteers." (University of Toronto, publ. in *Clinical Toxicology* 24 (5): 403 - 413 (1986)) Seven adult male volunteers were dosed with 1 ml/kg of a 3% sodium bromide solution (30 mg/kg bromide) after an overnight fast, three initially by the oral route and 4 by iv injection. Each subject was dosed twice, over a month apart. Serum concentrations of bromide were measured at 2, 3 and 4 hours and 3, 7 and 35 days. Oral bioavailability ranged from 75 - 118% with a mean of 96%. Differences between routes were not significant. T 1/2 was 11.9 days after oral administration and 9.4 days after iv administration. Supplemental information. No worksheet. (Gee, 10/29/01)

037 142038 Nishimura, H. and S. Miyamoto "Teratogenic effects of sodium chloride in mice." (Kyoto University, Japan, publ. in *Acta anat*. 74: 121 - 124 (1969)) Ten female mice of Japanese *dd* strain/group were given subcutaneous injections in the nape of the neck of 0, 1900 or 2500 mg/kg sodium chloride on day 10 or 11 of gestation. They were sacrificed on day 18 and the fetuses weighed and examined. The percent of dead or resorbed fetuses increased significantly in the treated groups as did the % malformed in survivors. Fetal body weight was significantly lower at 2500 mg/kg. The increase in osmotic pressure of the blood of fetuses may have been linked to the effects. Supplemental information. No worksheet. (Gee, 10/29/01).

037 142040 Oglesby, M. W., J. Rosenberg and J. C. Winter. "Behavioral and biochemical effects of chronic administration of bromide in the rat." (State University of New York, Buffalo, publ. in *Psychopharmacologia (Berl.)* 32: 86 - 92 (1973). CFN female rats were approximately 24 weeks of age at the start of sodium bromide treatment. At 8 weeks of age, 15 rats learned to drink from a dipper by depressing a lever. After a period of learning, rats were divided into 3 groups with mean matching times and treated for 7 days/week with bromide ion at 100, 200 or 300 mg/kg i.p. for six weeks. The bromide was replaced with water for an additional 4 weeks. The behavior testing was continued 5 days/week throughout the ten weeks. Injections were given post-trial. Effects of chlorpromazine on bromide depression were also studied by subdividing the groups. The rate of bromide excretion was measured after a dose 300 mg/kg for 6 days. Serum levels were measured at 4, 28, 76 and 100 hours following the last injection. Effects on norepinephrine and 5-hydroxytryptamine were also measured in the brain at each dose of bromide. The t 1/2 for excretion was calculated to be 55.5 hours. The response rate was increased at 100 mg/kg, markedly depressed at 300 mg/kg and highly variable at 200 mg/kg. Response rate increased to control levels on withdrawal of the bromide. Chlorpromazine did not antagonize bromide-induced rate depression. Brain levels of norepinephrine and 5-HT were not affected. Supplemental information. No worksheet. (Gee, 10/29/01).